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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/548,256	04/12/2000	Mylavarapu Venkatramesh	MTC 6462.1	6162

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SENNIGER POWERS LEAVITT AND ROEDEL
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EXAMINER
KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 07/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/548,256	VENKATRAMESH ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *14-17,20-33,43-45 and 49-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17-19,34-42,46-48 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor. Citizenship for 1st, 2nd, 3rd, and 5th – 10th inventors are omitted.

Specification

2. The abstract of the disclosure is objected to because it does not reflect the claimed invention e.g. steroid 5α-reductase nucleic acid. Correction is required. See MPEP § 608.01(b).

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed e.g. steroid 5α-reductase.

Election/Restrictions

4. Applicant's election with traverse of Group II, claims 1-13, 17-19, 34-42, 46-48, and 70 in Paper No. 17, filed 5/6/02 is acknowledged. The traversal is on the ground(s) that all the groups could all be searched together under one large simultaneous search and would not present any undue search burden, and that many of the groups have the same classification, and some of the groups constitute a Markush group. This is not found persuasive because the groups themselves comprise unique DNA sequences encoding functionally distinct enzymes that would each require a distinct search. Hence, the DNAs and plants comprising them, do not constitute a

Markush group. Restriction is not based on classification alone, but rather on recognized divergent subject matter, search required, and other factors as articulated in the restriction requirement mailed 12/5/01. Claims should be amended to delete nonelected subject matter.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 14-16, 20-33, 43-45, and 49-69 are withdrawn from consideration as being directed to a non elected invention.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-13, 17-19, 34-42, 46-48, and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a recombinant DNA construct comprising a sequence encoding a steroid 5α-reductase, transformed host cells, methods of making plants transformed with said recombinant construct wherein the seeds of said transformed plants have oil with elevated levels of sitostanol, sitostanol ester, or mixtures thereof; or phytosterol, phytosterol esters, or mixtures thereof when compared to untransformed plants, and the transformed plants thereof.

Applicant describes full length cDNA encoding steroid 5α-reductase enzymes, SEQ ID NO: 2 and 4, from *Arabidopsis* and corn respectively, and partial cDNA sequences encoding steroid 5α-reductase enzymes from soybean, SEQ ID NO: 6 and 8 (page 100, line 30).

Applicant does not describe other DNAs that encoding all other steroid 5α-reductase enzymes from all organisms as broadly claimed. Therefore, it is not clear that Applicant was in possession of the invention as broadly claimed.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-13, 17-19, 34-42, 46-48, and 70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is enabling only for claims limited to recombinant constructs comprising *Arabidopsis* and corn cDNAs encoding steroid 5α-reductase of SEQ ID NO: 2 and 4, as well as transformed host cells, transgenic plants and seeds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant claims a recombinant DNA construct comprising a sequence encoding a steroid 5α-reductase, transformed host cells, methods of making plants transformed with said recombinant construct wherein the seeds of said transformed plants have oil with elevated levels of sitostanol, sitostanol ester, or mixtures thereof; or phytosterol, phytosterol esters, or mixtures thereof when compared to untransformed plants, and the transformed plants thereof.

Applicant teaches full length cDNA encoding steroid 5α-reductase enzymes from *Arabidopsis*, Soybean, and Corn (Example 2 page 100, line 30), Applicant further teaches prophetically enhancement of sitostanol content in seeds of transgenic plants in transgenic plants engineered to express a 3-hydroxysteroid oxidase and a steroid 5α–reductase and their analysis by gas chromatography (Example 2 pages 100-101) and enhancement of sitostanol content in seeds of transgenic plants in transgenic plants engineered to express a 3-hydroxysteroid oxidase, a steroid 5α–reductase and a tocopherol biosynthetic enzyme and their analysis by gas chromatography (Example 7 pages 110).

Applicant does not teach how the DNAs were isolated nor how to isolate other DNAs that encode all other steroid 5α-reductase enzymes. Also, Applicant does not teach methods of making transformed plants, or seeds thereof, having increased levels of sitosterol, sitostanol ester, or mixtures thereof; or phytosterol, phytosterol esters, or mixtures thereof when compared to untransformed plants.

The metabolic and/or phenotypic effect of expression of transgenes in plants is highly unpredictable. For example, potato transformed with cystathione beta-lyase (CbL) with the intent of increasing the metabolic flux of sulfur metabolism toward the production of methionine, showed overexpression of CbL with respect to transcripts and protein but had no increase of

aspartate derived metabolites such as amino acids or pathway intermediates notably methionine (Maimann *et al.*, Enhanced cystathione beta-lyase activity in *transgenic potato* plants does not force metabolite flow towards methionine, Planta, 2001 Dec., 214 (2), 163-70, see especially Abstract, lines13-16). Furthermore, an important consideration in genetic engineering for over expression is knowing whether the enzyme is rate limiting and under some kind of regulatory control or influenced by additional mechanisms governing metabolic flux (Broun *et al.* PNAS July 31, 2001 vol. 98 pp8925-8927; see page 8926 second column, 2nd paragraph). Further, the isolation of orthologous DNA sequences from other species introduces an element of unpredictability. The limitation is introduced in finding homologous regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or a probes with limited homology. Thus the screen for orthologous sequences would isolate many genes other than those of interest.

Determining which, if any steroid 5α-reductase DNA sequences result in overproduction of sterols and tocopherols in transformed plants would require screening a myriad of constructs comprising different DNAs encoding steroid 5α-reductase and plants transformed therewith. The measurement of relative increases in sterols and tocopherols from seeds in transformants would require trial and error experimentation since no guidance is provided in the specification for screening for the particular phenotype that would arise from over expression of steroid 5α-reductase. The isolation of orthologous cDNAs encoding steroid 5α-reductase would require making and testing of degenerate PCR primers and probes, as well as making and screening a multitude of cDNA libraries with those probes to isolate other cDNAs encoding steroid 5α-reductase. The testing of the putative positives would entail screening through a host of false

positives to isolate other cDNAs encoding steroid 5α-reductase. Therefore undue experimentation would be required for one of skill in the art.

Given the lack of guidance for isolating DNA sequences encoding steroid 5α-reductase and producing plants with increased sterol and sterol ester levels in the specification that reflect the breadth of the claims, and the unpredictability in the art, undue trail and error would be needed to practice the invention. Therefore, the invention is not enabled for the scope set forth in the claims.10

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2-6, 17-19, 34-35, 38-42, 46-48, and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 2, "which, when said promoter is a seed specific promoter" is indefinite. It is unclear if the promoter is seed specific or not.

At Claim 3 and 4, "which, when said promoter is a seed specific promoter" is indefinite. It is unclear if the promoter is seed specific or not.

Claim 5 comprises improper Markush language.

At Claim 5, line 2, "consisting of a site derived" is indefinite. It is unclear if the site is the same as the source or not.

Claims 17-19, 34-35, 38-40, 46-48, and 70 are dependent on nonelected claims.

At Claim 38, line 3, "conductive" and "contain" should be --conducive-- and --containing--.

At Claim 39, and 2, "conductive" should be --conducive--.

Claim 42 contains improper Markush language.

Claims 46-48, "when said regulatory signals cause seed specific expression" is a meaningless limitation because it does not further limit the claims.

Claims 46-48, "said enzyme encoding DNAs" lacks proper antecedent basis.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claim 34, 35, 37 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed inventions encompass untransformed plants and seed, which are a product of nature and not one of the five classes of patentable subject matter. Claim 41 is drawn to the progeny of the transformed plant. Due to Mendelian inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only two thirds of the progeny having at least a single copy of the transgene and one quarter of the progeny would not carry a copy of the transgene. Since the claim encompasses progeny that lack the transgene, the claim encompasses plants that are indistinguishable from plants that would occur in nature. See *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 76 USPQ 280 (1948), and *In re Bergy , Coats, and Malik* 195 USPQ 344, (CCPA) 1977. Amendment of the claims to recite that the progeny comprise the construct that was introduced into the parent plant would overcome the rejection.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 7-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Li *et al.* (PNAS Vol. 34, pp.3555-3559, April 1997).

Li teaches a recombinant construct and plant expression vector comprising operably linked components in 3`-5` orientation, the CaMV 35S promoter which is functional in a plant plastid, a DNA sequence encoding a steroid 5α-reductase enzyme, and a transcription termination signal sequence, (page 3555 column 1, lines 32-46). Li also teaches a transformed host cell, particularly a plant cell, and a plant with at least one transformed cell (page 3556 column 2, lines 33-34), and seed with at least one transformed cell (page 3556, column 2, lines 57-61). Thus, Li discloses all the limitations of instant Claims 1, and 7-12.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1 and 3-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (PNAS Vol. 34, pp.3555-3559, April 1997) in view of Maliga *et al.* (U.S. Patent 5,530,191).

The teachings of Li are discussed supra; Li also teaches selection on kanamycin (p. 3555, left hand column), and hence inherently teaches that said recombinant construct comprises a selectable marker DNA.

Li does not teach said recombinant construct comprising, DNA regions homologous to the genome of said plant flanking the plant expression cassette, nor a phage T7 gene 10 leader sequence and ribosomal binding site.

Maliga teaches plant plastid transformation with a recombinant construct comprising a promoter functional in a plant plastid (column 5, lines 61-64), DNA regions homologous to the genome of said plant flanking the plant expression cassette (column 8, lines 51-57), a phage T7 gene 10 leader sequence and ribosomal binding site (column 5, lines 64-67).

It would have been *prima facie* obvious at the time of Applicant's invention to modify the invention of Li to substitute the plastid transformation/expression cassette elements as taught by Maliga in the recombinant construct taught by Li. One would have been motivated by the teaching of Li that plant transformation with a DNA sequence encoding a steroid 5α-reductase enzyme was generally useful for genetically modifying plants for altered growth and by Maliga that plastid transformation allows for combination of characteristics that are either difficult or impossible to combine. Hence, one would have had a reasonable expectation of success.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-2, and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (PNAS Vol. 34, pp.3555-3559, April 1997) in view of Falco *et al.* (Bio-Technology 1995, Vol. 13, no. 6, pp. 577-582; see Abstract, lines 4-8).

The teachings of Li are discussed supra;

Li does not teach said recombinant construct comprising, a transit peptide expressed from a seed specific promoter.

Falco teaches transformation of canola and soybean with a plant expression cassette that comprises a DNA encoding either a feedback regulation insensitive bacterial dihydrodipicolinic acid synthase or aspartokinase, a seed specific promoter, and a chloroplast transit peptide resulting in an increase in free lysine in the seed of canola and soybean.

It would have been *prima facie* obvious at the time of Applicant's invention to modify the invention of Li to include the seed specific promoter and transit peptide taught by Falco in the transformation method taught by Li. One would have been motivated by the teaching of Li that plant transformation with a DNA sequence encoding a steroid 5α-reductase enzyme was generally useful for genetically modifying plants for altered growth and that modification of seed metabolism was useful as taught by Falco. Hence, one would have had a reasonable expectation of success.

19. All claims are rejected.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Kim Davis, whose telephone number is (703) 308-0009.

Russell Kallis Ph.D.
July 16, 2002

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